

The New York Times**Science****Variant Gene Tied to a Love Of New Thrills**

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Maybe it is appropriate that the first gene that scientists have found linked to an ordinary human personality trait is a gene involved in the search for new things.

Two teams of researchers have reported detecting a partial genetic explanation for a personality trait called "novelty seeking." People high in a novelty-seeking quotient tend to be extroverted, impulsive, extravagant, quick-tempered, excitable and exploratory -- your flamboyant Uncle Milton who shows up with an armload of presents, bellows his hellos, pretends to pull coins from your ear, knows all the latest disaster jokes and then sits around after the family dinner looking faintly bored.

Reporting yesterday in the journal *Nature Genetics*, the scientists said they had discovered that novelty seekers tend to have a particular variant of a gene that allows the brain to respond to dopamine, an essential chemical communication signal. The gene encodes the instructions for the so-called D4 dopamine receptor, one of five receptors known to play a role in the brain's response to dopamine. As it turns out, novelty seekers possess a version of the D4 receptor gene that is slightly longer than the receptor of more reserved and deliberate individuals.

In theory, the long gene generates a comparatively long receptor protein, and somehow that outsized receptor influences how the brain reacts to dopamine.

Dr. Richard P. Ebstein and his colleagues at Herzog Memorial Hospital in Jerusalem and at Ben-Gurion University in Beersheva, Israel, wrote one of the papers. The other comes from Dr. Jonathan Benjamin, Dr. Dean H. Hamer and their colleagues at the National Institutes of Health in Bethesda, Md.

Dopamine is only one of many so-called neurotransmitters found coursing through the brain, sharing its chemical communication duties with such other renowned neurotransmitters as serotonin and norepinephrine. However, dopamine is the chemical most strongly linked to pleasure and sensation seeking.

Recreational drugs like cocaine, nicotine and alcohol are thought to act through the brain's dopamine system. Conversely, people with Parkinson's disease, in which the dopamine-producing cells of the brain gradually degenerate, have been shown to be unusually low in novelty-seeking behavior. Hence, the dopamine system has long been proposed as an actor in impulsive, extravagant behavior.

The new report of the genetic link to the D4 receptor, though, is the first clear evidence of a connection between the neurotransmitter and the personality type.

It is also the first known report of a link between a specific gene and a specific normal personality trait, Dr. Ebstein said in an interview. Other reports have tentatively linked genes to behavioral pathologies like schizophrenia or alcoholism, but a taste for the novel is neither good nor bad, merely a color on the prism of ordinary human complexity.

The gene does not entirely explain the biological basis for novelty seeking. Research on animals, as well as extensive studies of human twins of both the identical and fraternal variety, indicate that about half of novelty-seeking behavior is attributable to genes, the other half to as-yet ill-defined environmental circumstances. Scientists say the dopamine receptor accounts for perhaps 10 percent of the difference in novelty-seeking behavior between one person and the next.

"If we assume there are other genes out there that we haven't looked at yet, and that each gene exerts more or less the same influence as the D4 receptor," said Dr. Ebstein, "then we would expect maybe four or five genes are involved in the trait."

The influence of the receptor variance on behavior may be modest, but the strength of the new finding is considerable. Not only did the two groups find the same correlation between receptor length and novelty seeking, but they found it in different ethnic groups -- the Israeli subjects being mostly Ashkenazi and Sephardic Jews of both sexes, and the group in the United States made up mainly of white American (and presumably genetically diverse) men.

In both studies, the researchers determined their subjects' degree of novelty-seeking behavior by giving them personality inventories. Participants were asked to answer yes or no to 100 or more questions, among them queries like, "I'm confident everything is going to be O.K., even in situations that would worry others," or "I like to experience new things for the simple enjoyment or thrill of it, even if most people

think this is a waste of time."

The researchers also took blood samples from their subjects, isolated the DNA within the blood cells, and measured one segment, or exon, of the D4 dopamine receptor gene. The exon was known to vary in length among different healthy populations, exhibiting anywhere from 2 to 10 so-called repetitions of DNA subunits.

The scientists discovered that those subjects having a high number of exon repetitions were significantly more likely to rate as impulsive, quick-tempered, fickle, curious and extravagant than those with fewer repetitions.

"This is a very credible finding, given the strength of replication by different groups in different countries," said Dr. C. Robert Cloninger of the Washington University School of Medicine, who first proposed a link between dopamine and novelty-seeking behavior 10 years ago. "This does account for only a small percentage of variance in one aspect of temperament, but it shows what can be done. And more work like this will definitely be done." Dr. Cloninger wrote a commentary that accompanies the two reports.

Novelty seeking is one of four aspects that Dr. Cloninger and many other psychologists propose as the basic bricks of normal temperament, the other three being avoidance of harm, reward dependence and persistence. All four humors are thought to be attributable in good part to one's genetic makeup -- the predisposition that one is dealt at birth. They are the aspects of human nature that mark one person as a pessimistic worrywart, another as an outgoing team player.

Temperament remains fairly stable throughout life, Dr. Cloninger said, which means the shy and anxious boy is likely to be the shy and anxious grandfather, though psychiatric drugs, intense counseling or life-changing experiences can modify some aspects of temperament.

Any one person may have a mixture of varying degrees of the four temperamental dimensions. For example, a novelty seeker may have a low quotient of harm avoidance, not fretting over dangers real or imagined; a high level of persistence, and a high level of reward dependence, and so cares about making some sort of impact or statement.

Such an individual could serve as a poster person for achievement, the type with the self-confidence, optimism and originality to do something brilliant in life, assuming his or her great temperament was combined with great talent.

Alternatively, a novelty seeker who is low in reward dependence and low in harm avoidance may care little for friends or society and end up an aloof alcoholic.

The heritability, or genetic component, of the four temperament dimensions was roughly calculated based on studies of identical twins who shared all their genes and fraternal twins who shared only about half their genes. In some cases, the identical twins being analyzed were reared apart, and so were subject to presumably distinct environments while their temperaments were being forged.

Dr. Cloninger said that while the environment exerted considerable effect on temperament, it was not the environment that people normally thought of in the endless debates over nature versus nurture.

He said that parents had little influence on their children's temperaments. Instead, it is the random experiences and circumstances that an individual encounters in childhood, the chance exposures to reward or punishment, that may strengthen or weaken one's innate tendency toward avoidance of harm, novelty seeking and the like.

Where parents do have a major effect on their children, Dr. Cloninger said, is in character formation. "Parents can influence children's attitude toward themselves and other people, their capacity for empathy, their goals and values," he said.

Parental attitudes also help a child mature into a reasonable adult. "Knowing someone's temperament doesn't tell you whether the person is mature or immature," Dr. Cloninger said. "That's an issue of character development." A child may not be born a tabula rasa, but there are plenty of edit keys at a parent's command.

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